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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/557,907	04/21/2000	Holly Horton	1530.0060004/EKS/EJH	9397

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EXAMINER	
WILSON, MICHAEL C	13

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/557,907	Applicant(s) HORTON ET AL.	
	Examiner Michael Wilson	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-103* is/are pending in the application.

4a) Of the above claim(s) *11-14,19-28,36,37,51-65,76 and 88-103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,15-18,29-35,38-50,66-75 and 77-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 & 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group I, claims 1-35, 38-50, 66-75 and 77-87 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the burden required to search both inventions together would not be undue. This is not found persuasive. Determining whether a reference teaches the limitation of 20-300 mM sodium phosphate is time intensive because such a search cannot be performed by a simple word search. In non-patent literature, such a limitation is not included in searchable terms. Non-patent literature must be obtained that potentially teaches the sodium phosphate conditions used to transfect cells and a determination made as to how the reference correlates to the limitation. In patent literature, the term sodium phosphate may be searched, but the large numerical range cannot be searched by a word search. Furthermore, the concentration may be expressed in different units (e.g. M, not mM). Overall, each reference must be reviewed individually to determine the concentration of sodium phosphate. The examiner attempted to search both inventions together and determined that the burden was undue. The requirement is still deemed proper and is therefore made FINAL.

Applicants note that claims 66-87 should not have been included in Group II. Applicants argument is persuasive.

Claims 51, 57, 65, 76, 88 and 95 were withdrawn because they encompass RNA. Claims 36, 37, 52-56, 58-64, 89-94 and 96-103 are withdrawn because they require 20-300 mM sodium phosphate. Claims 11-14 and 19-28 are withdrawn because they do not encompass interferon α

(37 CFR 1.142(b)). Applicant timely traversed the restriction (election) requirement in Paper No. 12. Claims 1-10, 15-18, 29-35, 38-50, 66-75 and 77-87 are being examined as they relate to administering DNA encoding INF-α.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-10, 15-18, 29-35, 38-50, 66-75 and 77-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering a plasmid intramuscularly to a mouse having a tumor, wherein said plasmid comprises a nucleic acid sequence encoding INF-α operably linked to a promoter, wherein said administering causes a decrease in tumor volume, a decrease in tumor metastases and an increase in survival, does not reasonably provide enablement for any non-infectious, non-integrating DNA, any active fragment of INF-α, DNA encoding INF-α that is not operably linked to a promoter, administering the composition to smooth muscle or myocardial tissue, obtaining cell-, tissue- or tumor-specific expression of INF-α, administering a vector encoding INF-α as well as another cytokine or treating any symptom of cancer as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The state of the art with respect to INF-α and cancer therapy at the time of filing can be well established in review articles published by Henderson (1992, Trends Pharm. Sci., Vol. 13, pages 145-152), Sedlacek (Critical Reviews in Oncogenesis, Vol. 5(6): 555-587, 1994), Dalgleish (Cancer Surveys, Vol. 26: 289-320, 1995), Belldegrun (1993, J. NCI, Vol. 85, pages 207-216), Santodonato (Jan. 1, 1996, Human Gene Therapy, Vol. 7, pages 1-10), Kaido (1995, Int. J. Cancer, Vol. 60, pages 221-229), Zhang (April 1996, PNAS, Vol. 93, pages 4513-4518), Zhang (1996, Cancer Gene Therapy, Vol., 3, pages 31-38) and Pestka (WO 97/00085, Jan. 3, 1997).

Henderson reviewed the properties of INF-α (page 146, Table 1). Sedlacek provided a review of treatment of tumors in general and detailed descriptions of immune pathways known to be generated by various cytokines (see pages 568-575). Sedlacek emphasized the difficulty in treating tumors due to their resistance to immune recognition (see abstract and page 571, column 1, first full paragraph). Sedlacek specifically indicated that the combination of methodologies required to generate a specific immune response against tumors has not yet been discovered (page 575). Dalgleish reviewed the importance of INF-α in generating tumor specific immune responses (page 299, line 6), and indicated that "different cytokines can induce different anti-tumor immune responses offers boundless opportunities for combination as well as the potential for synergy" (pages 298-230). Pestka taught using tumor cells transfected with a plasmid encoding IFN-α to treat cancer (page 44, line 15).

Specifically, Belldegrun taught renal carcinoma cells transfected with a plasmid encoding INF-α had decreased tumorigenicity in mice as compared to non-transfected cells. Santodonato taught administering Friend erythroleukemia cells (FLC) comprising a plasmid encoding INF-α to pre-established FLC tumors caused tumor inhibition (page 3, col. 1, 11 lines from the bottom). Kaido taught that melanoma cells transfected with a plasmid encoding INF-α had decreased tumorigenicity in mice as compared to non-transfected cells. Zhang taught that a number of tumors transfected with a retroviral vector encoding INF-con1 had decreased tumorigenicity in mice as compared to non-transfected cells. INF-con1 has significant homology to INF-α and shares the most frequent amino acids in eight of the different IFNs (page 31, 12 lines from the bottom). Thus, it is clear from the prior art that the potential for treating various tumors using DNA encoding INF-α existed.

At the time of filing, the combination of vector, promoter, protein and route of administration required to obtain a particular effect and to target desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems

hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate the combination of vector, protein, promoter and route of administration required to obtain the desired effect and to target desired cells is unpredictable (see entire article; page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Roth (1997, J. National Cancer Inst., Vol. 89, pages 21-39) taught non-viral vectors did not target cells of interest and provided low efficiency (page 26, col. 2).

The specification teaches making plasmids VR4101 and 4111 which encode mouse α and VR4102 and VR4112 which encode human IFN-α (page 92, line 24 - page 93, line 9). The plasmids were administered to mice having established melanoma, glioma or epidermoid carcinoma intramuscularly (page 100, line 33 - page 101, line 16; page 101, line 29). IFN-α was expressed to detectable levels in the serum in mice injected five times intramuscularly with 100 μl of VR4111 (page 103, line 13). Fig. 3 and 4 show mice having melanoma, glioma or

epidermoid carcinoma receiving plasmid encoding mouse IFN-α intramuscularly experienced a decrease in tumor volume and an increase in survival as compared to control mice (page 104, line 11-22). Fig. 6 and 7 show mice having melanoma and epidermoid carcinoma metastases receiving plasmid encoding mouse IFN-α intramuscularly experienced a decrease in metastases as compared to control mice (page 105, line 18 - page 106, line 12).

The specification does not compare plasmids to other vectors such that one of skill could use administer any non-infectious, non-integrating DNA encoding IFN-α as broadly claimed to treat cancer or metastases. It is not clear that other vectors would have the same tissue targeting or express IFN-α to an amount that is therapeutic. Given the lack of predictability in the art regarding the combination of elements required to obtain the desired effect taken with the teachings in the specification, the only non-infectious, non-integrating DNA that is enabled in the claimed method is a plasmid.

The specification does not teach any active fragment of IFN-α that would treat cancer or metastases, specifically to decrease tumor, increase survival or decrease metastases. The art at the time of filing and the specification do not teach fragments of IFN-α capable of treating cancer or metastases. The specification does not provide an assay for determining the IFN-α fragments that are capable of treating cancer or metastases. Without such guidance, the specification does not enable fragments of IFN-α capable of treating cancer or metastases as claimed.

The specification does not enable using the invention where the DNA encoding IFN-α that is not operably linked to a promoter. For IFN-α to be expressed, it is essential that the DNA

encoding IFN-α be operably linked to a promoter. The specification does not teach how to express IFN-α in the absence of a promoter. Therefore, the claims should recite that the DNA encoding IFN-α is operably linked to a promoter as in claims 75 and 87.

The specification does not enable administering the composition to smooth muscle, myocardial tissue (claim 7), any body cavity (claim 66 and 78) or the peritoneal cavity (claims 70 and 81). The art at the time of filing and the specification does not teach administering plasmid encoding IFN-α to smooth muscle, the myocardium, the peritoneal cavity or any other body cavity. The specification teaches intramuscular injection to striated muscle which results in systemic delivery of the plasmid. The specification does not correlate intramuscular injection to striated muscle to injecting smooth muscle, the myocardium, the peritoneal cavity or any other body cavity such that systemic delivery is obtained or cancer is treated. As such it cannot be determined whether injection into smooth muscle, the myocardium, the peritoneal cavity or any other body cavity would also result in myocardial cells expressing IFN-α. The specification and the art at the time of filing do not teach the effect of expressing IFN-α in smooth muscle, the myocardium, the peritoneal cavity or any other body cavity. Given the lack of predictability in the art regarding the combination of elements required to obtain a desired effect using gene therapy taken with the teachings in the specification, the specification does not enable administering DNA encoding IFN-α to smooth muscle, the myocardium, the peritoneal cavity or any other body cavity as broadly claimed.

The specification does not enable obtaining cell-, tissue- or tumor-specific expression of IFN-α (claims 44 and 45) or "selectively transfecting malignant cells" (claim 78). The specification teaches obtaining systemic delivery of IFN-α. The specification does not teach targeting IFN-α to a particular cell, tissue or tumor or the effect of such targeting. Given the lack of predictability in the art regarding targeting DNA to the desired tissue, taken with the teachings in the specification regarding the effect of targeting IFN-α to specific cells, tissues or tumors, the specification does not enable using cell-specific, tissue-specific or tumor-specific regulatory elements in the method as claimed.

The specification does not enable administering a vector encoding IFN-α as well as another cytokine (claim 42). The effect of IFN-α and another cytokine is not taught in the art at the time of filing or the specification. Given the lack of predictability in the art regarding the combination of elements required to obtain the desired effect using gene therapy taken with the lack of teachings in the specification regarding the effect of IFN-α and another cytokine, the specification does not enable using a plasmid encoding IFN-α and another cytokine as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-10, 15-18, 29-35, 38-50, 66-75 and 77-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 does not further limit claims 1 or 2 because the DNA is already administered into the muscle which is equivalent to "intramuscular" injection in claim 8. The limitation of intramuscular injection in claim 29 does not further limit claims 1 or 2 for the same reasons.

Claim 42 is indefinite because it is unclear what the phrase "operably encodes" means.

Claims 44 and 45 are indefinite because the metes and bounds of what applicants consider "cell specific" and "tissue specific" cannot be determined. It is unclear if the expression is limited to one cell, one particular type of cell, one area of a tissue or one particular type of tissue, or if expression is merely favored in one particular cell or tissue.

Claims 4 contains an improper Markush group. Head and neck cancer can be a number of the cancers listed such as melanoma. A solid cutaneous tumor can be a number of the cancers listed. Metastases of cancers listed such as melanoma can be prostate, ovarian, breast, lung, liver, bladder, uterine, bone or breast cancer. Clarification is required.

Claims 39 and 40 contain improper Markush groups because cationic peptides are cationic proteins. Cationic lipids, cationic peptides or cationic proteins are all cationic polymers.

Claim 42 is indefinite because the phrase "further comprises a DNA encoding one or more additional cytokines" is confusing. It is unclear whether applicants intend to claim a construct encoding IFN-α and a different cytokine or two copies of IFN-α.

Claim 46 is an improper Markush groups because gene therapy or immunotherapy can also be considered a type of chemotherapy. Gene therapy can also be considered a type of immunotherapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

3. Claims 1-10, 15-18, 29-35, 38-50, 66-75 and 77-87 are rejected under 35 U.S.C. 102(b) as being anticipated by Horton (Feb. 1999, PNAS, Vol. 96, pages 1553-1558).

Parent case 09/196,313 was not available at the time of writing the instant office action. Upon review of the application and until a proper determination of priority can be made, the following rejection is made in case parent case '313 does not enable the instant claims.

Horton taught administering plasmids encoding mouse and human IFN-α intramuscularly to mice having established melanoma, glioma or epidermoid carcinoma. IFN-α was expressed to detectable levels in the serum. The mice experienced a decrease in tumor volume and an increase in survival as compared to control mice. Mice having melanoma and epidermoid carcinoma metastases receiving plasmid encoding mouse IFN-α intramuscularly experienced a decrease in metastases as compared to control mice. The IFN-α comprises amino acids -23-166 of SEQ ID NO:10. Thus, Horton anticipates the claims.

4. Claims 66, 67, 69, 71, 75, 78-80, 83 and 87 are rejected under 35 U.S.C. 102(e) as being anticipated by Pestka (WO 97/00058, Jan. 3, 1997).

Pestka taught administering tumor cells subcutaneously to mice having tumors, wherein the tumor cells were transfected with a plasmid encoding IFN-α operably linked to a promoter, and obtaining a decrease in tumor (page 44, line 15). Thus, Pestka teaches all the limitations of the claims.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER